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Semen quality as a potential susceptibility indicator to SARS-CoV-2 insults in polluted areas

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Abstract

High levels of air pollution can contribute to high rate of the COVID-19 outbreaks. Air pollutants induce oxidative stress, inflammatory process, immune imbalance and coagulation at systemic level, making the organism susceptible to complications caused by various pathogens, including viruses, resulting in a possible important damage co-factor. Sperm cells are highly sensitive to the pro-oxidant effects of environmental pollutants, and may represent an important alarm bell indicating that the burden of environmental pressure in a certain area is causing damage to humans. A comparison of the maps of COVID-19 case fatality rates, male infertility rates and air pollution may suggest a way to understand the dynamics of the virus impact. Semen quality may be considered as an early and sensitive environmental marker, and also a potential susceptibility indicator to viral insults (including SARS-CoV-2) in heavily polluted areas. Therefore, assessing the burden of environmental exposure of a given population and its potential susceptibility to insults through early biological stress indicators may be helpful for predicting the risk of the adverse effects by the SARS-CoV-2 epidemic .

Key words: air pollution, COVID-19, semen quality, environmental marker, health marker, oxidative stress, SARS-CoV-2

Air pollution and COVID-19

A recent review point out that chronic exposure to air pollutants in the most polluted areas of the world leads to more severe and lethal forms of COVID-19[1]. Indeed, a preprint study, carried out in 3,080 counties in the United States calculated an 8% increase in the COVID-19 death rate adjusted by 20 potential confounding factors for 1 microgram/m^3 elevation of fine particulate matter with a diameter of 2,5 µm or less ($PM_{2,5}$)[2]. Furthermore, in 2003, during SARS infection in China, scientists reported that Case Fatality Rate (CFR) in the most polluted areas was twice as high as in the least polluted ones[3]. Another preprint study has reported a higher CFR of COVID-19 in Wuhan, China, with increasing of air particular matter with diameter of 10 µm or less (PM_{10}) and $PM_{2,5}$ after adjusting for humidity and temperature[4]. Moreover, some authors pointed out that the regions of Northern Italy most affected by COVID-19, were among those with the highest levels of PM_{10} and $PM_{2.5}$ in Europe[5–7]. A recent preprint found a significant correlation between high levels of $PM_{2,5}$, carbon monoxide (CO), nitrogen dioxide (NO_2) and COVID-19 spread and mortality in Italy, U.S.A. and China[8].

COVID-19 spread after initial outbreaks (China, South Korea, Iran) occurred in Italy before that observed in the rest of Europe and Eastern U.S.A., between latitude 30° and 50° North, in Winter (December to April), when weather patterns, such as low temperature (between 5 and 11 °C) and low specific and absolute humidity of 3-6 g/kg and 4-7 g/m^3 respectively were favourable for the spread of a respiratory virus[9]. Furthermore, it is significant that in the same seasonal period (May for Brasilian winter) the highest local peak out of this belt is in Sao Paulo, Brazil, a heavily polluted city (figure 1)[10]. It's known that in the winter period the air pollution rates are higher and the cities where COVID-19 has hit hardest are those with PM_{10}, $PM_{2,5}$ and NO_2 annual average above the WHO recommended values of 20 µg/m^3, 10 µg/m^3 and 40 µg/m^3 respectively (figure 1)[11–17]. Stability of SARS-CoV-2 in different environmental conditions supports the hypothesis that air pollution may favour the human-to-human chain of transmission of the infection, particularly in elevated crowding situations, COVID-19 severity and risk of related death[1,18].

Pollution and susceptibility to viral insults

The World health Organization (WHO) estimates that about a quarter of diseases is due to prolonged exposure to environmental pollutants[19,20], including cardiovascular and chronic degenerative disease, premature deaths and reproduction dysfunctions[19,21–23] along with lifestyle, as reported in the European Code against Cancer[24]. Moreover, environmental pollutants can increase susceptibility to non-communicable diseases (NCDs) and determine a significant decline in body's defences, possibly due to also transgenerational effects that may partly explain the worldwide disease burden consisting not only in non-communicable but also communicable diseases (dengue, yellow fever, tuberculosis, etc.)[24–36]. Furthermore, it shows that this is transmitted to the following generations, by reducing the defence ability toward viral pathogens[26].

In particular, the chronic exposure to the air-born finest fraction of particulate matter ($PM_{2.5}$), not only induces inflammation to alveolar district, but, passing the alveolar barrier, it reaches the blood and hence the peripheral tissues, inducing oxidative stress both directly and through the guest response to the chemical insult. This contributes to the activation of inflammasome and, particularly, NLRP3, influencing the maturation and secretion of Cytokine such as IL-1 beta and IL-18 both involved in the systemic inflammatory syndrome and in the conditions facilitating the pathogen agent virulence, including vascular leakage and coagulopathy[37–40].

SARS-CoV-2 is able to unleash a fast process of autoimmune dysregulation, by inducing a significant Cytokine storm, mainly TNF-α, IL-6 e IL-1β, IL-17, IL-18, in genetically predisposed individuals[41]. Such a process could be even more important when pre-existing environmental factors have already altered regulatory mechanisms for Cytokine release and/or even when there are some polymorphisms for IL-6, such as in specific populations or ethnic groups who in fact make them more susceptible to virus complications[42]. Specifically, all populations are susceptible to COVID-19, but the elderly, individuals with chronic diseases or low immune defences, pregnant women and newborns are most exposed to complications[43–45].

In addition, air pollutants induce oxidative stress, inflammatory process, immune imbalance and coagulation at systemic level, making the organism susceptible to complications arising from the pathogen agents, including SARS-CoV-2, resulting as a possible important damage co-factor[46].

This is even more true in those areas of the world where poor air quality (figure 2) could, favour viral contagion and/or increased virulence, decreasing the antioxidant and immune defences of the organism.

Sperm decline in polluted areas

Many data suggest a decline in sperm parameters in different areas of the world, particularly in developed ones or those undergoing strong industrial development with high levels of air pollution[47]. A systematic review and meta-regression analysis reported a decline of total sperm counts by 59.3% in Europe, U.S.A., Canada and New Zealand between 1971 and 2011[48]. In Asia, the infertility rate of Iranian men has increased by 20% over the last 20 years and in China, out of a total of 30,636 young donors, the sperm concentration and percentage of sperm with normal morphology decreased from 68 × 106/mL to 47 × 106/mL and from 31.8% to 10.8%, respectively[49,50]. In Brasil, in the past 23 years a median reduction of 0.24 million/mL of spermatozoa per year was reported[51].

The male reproductive system is, indeed, extremely sensitive to environmental pollutants. In particular, chronic exposure to high levels of PM_{10}, $PM_{2.5}$ and individual air pollutants such as NO_2 and sulfur dioxide (SO_2) are negatively associated with sperm count, motility and testicular volume in infertile subjects[52,53]. The mechanisms of spermatogenesis damage by environmental agents are largely unknown, although radical oxygen species (ROS) imbalance and associated oxidative stress may be the common denominator through which pollutants alter the most sensitive parameters of seminal quality such as sperm count, motility, morphology and integrity of sperm DNA[54–56]. As a matter of fact, sperm cells are highly sensitive to the pro-oxidant effects of environmental pollutants, due to the limited volume of the cytoplasmic space, with less antioxidant defence, and sperm membrane lipids are target of ROS[57]. In this regard, we recently reported that male gametes are the most sensitive cells to the accumulation of damaged DNA and showed, through molecular investigations, that the sperm nuclear basic proteins from samples of men living in polluted areas have a new and unexpected behaviour, resulting involved in DNA oxidative damage[58]. The COVID-19 CFR map of the most important outbreaks in the world areas presenting, in recent decades, a negative trend in sperm quality, together with the average annual levels of PM_{10}, $PM_{2.5}$ and NO_2, shows a certain overlapping (figure 1). It could be argued that sperm decline may represent the earliest clinical sign of environmental pressure.

Human semen as environmental and health marker

We and other authors indicate human semen as a “sentinel biomarker” of subclinical biological effect suitable for monitoring the impact of adverse environmental exposures[59-63].

Semen quality has also been found to reflect individuals’ general health condition, as recent studies showed an association between semen quality and the onset of chronic diseases, with male infertility as a predictor of future hospitalization and overall mortality[64-68].

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We speculate that this observation could help understanding the dynamics that may have facilitated the COVID-19 severity in polluted areas. As an early and sensitive environmental and health marker, semen quality could be considered as a potential susceptibility indicator of external insults to the health of the general population and be used for health risk management, innovative prevention programs and health surveillance, especially in heavily polluted areas[62,63]. However, although high population density (according for human-to-human transmission mechanisms), climatic characteristics, age, comorbidity, different capacity of health systems to face the pandemic and prevention policies adopted in the various countries currently play the central role, we should not overlook the possible facilitating contribution of pollution in increasing the risk for people living in areas with higher environmental pressure to the COVID-19 impact. Moreover, it must be considered that higher incidence of non-communicable diseases (NCDs) and male infertility are reported in these same areas because of a complex interaction between factors of chronic chemical and physical exposure, along with the contribution of lifestyle behavioural risk factors and individuals' genetic background. In particular, human sperm decline in the last decades, represent an important alarm bell indicating how the burden of environmental pressure is becoming increasingly unsustainable. In this perspective, the first signs of damage to organo-sentinel systems such as the male reproductive system, detectable by the reduction in semen quality over time can be an opportunity to know the health status of the population in a given environmental context, including susceptibility to the virus impact in that population, and predict the medium to long term adverse effects on human health.

However, in our opinion semen quality as an early environmental and health marker could help the policy makers to intervene promptly in areas with significant environmental criticalities in order to reduce air, water and soil pollution with an integrated approach in a One Health perspective, where the sharing of information between different professional figures (clinicians, biologists, chemists, virologists, veterinarians, economists, epidemiologists) can succeed to find a systemic approach that could be effective on a global scale[69]. Above all, it is necessary to estimate effectiveness of the measures adopted to safeguard the health of community and also its social and productive organization, with the aim to avoid, or at least reduce, the rapid and destructive spread of future viruses.

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Author contributions

LM developed the concept and drafted the manuscript, PMB collected the data, IMB, AG, FD and MP edited and revised manuscript, LM, IMB, FD, PMB, AG and MP approved the final version of the manuscript.

Competing interests

The authors declare no competing financial interest.

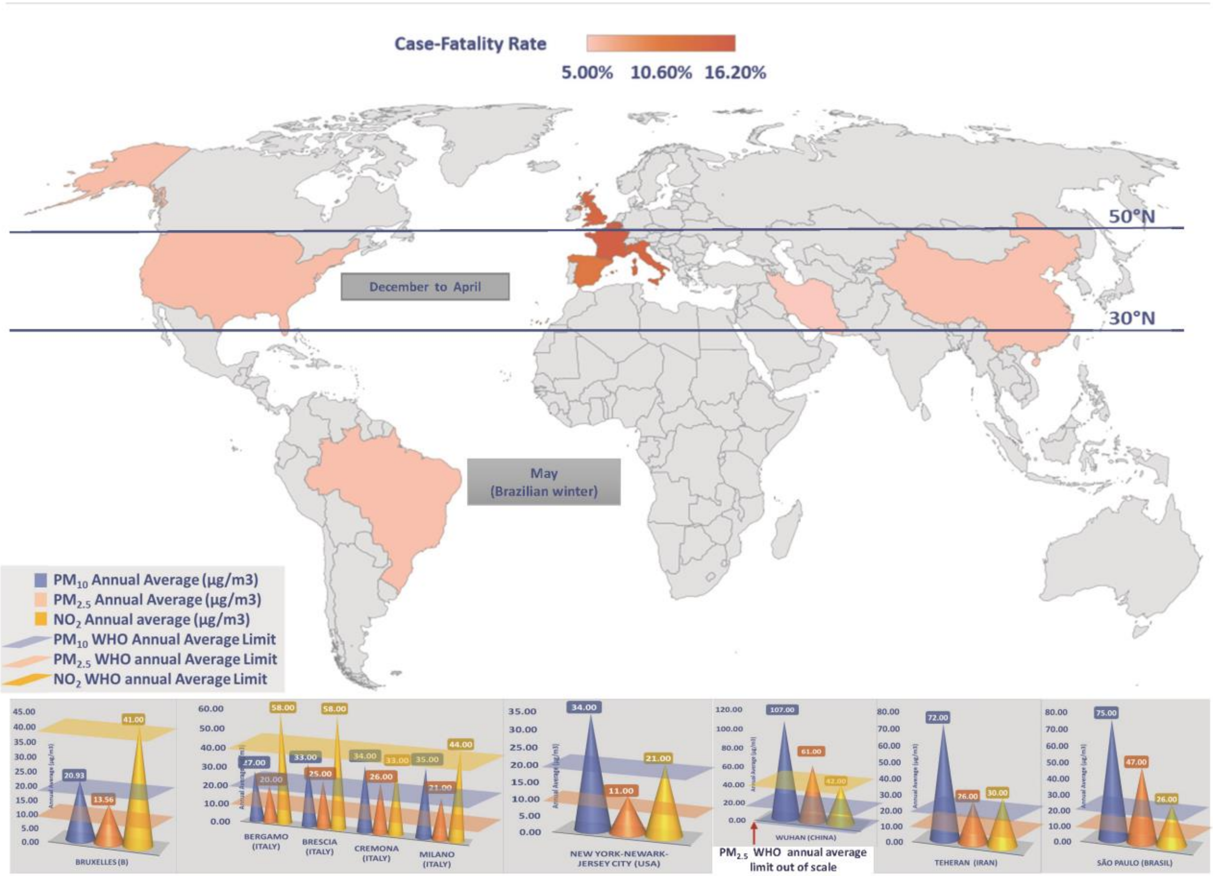

Figure 1: Overlapping between Case Fatality Rate maps (from pink to brown) of the most important COVID-19 outbreaks, air pollution and world areas presenting, in recent decades, a negative trend in sperm quality. Some cities of the same areas with PM_{10}, $PM_{2,5}$ and NO_2 annual average above the WHO recommended values of 20 µg/m^3, 10 µg/m^3 and 40 µg/m^3 respectively.

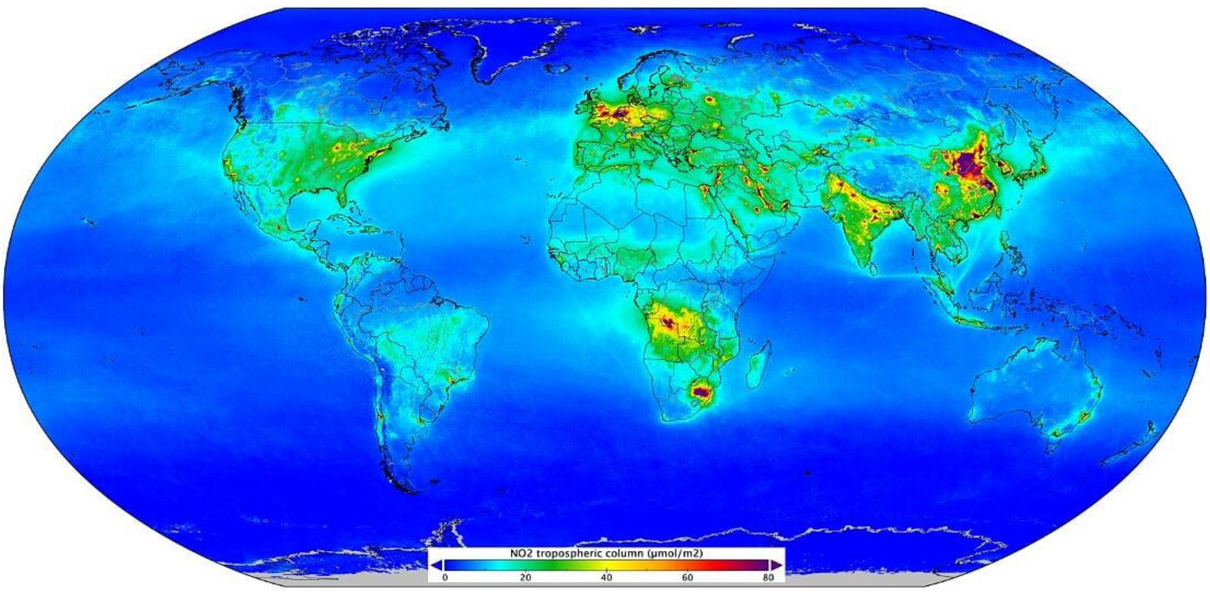

Figure 2: World map of tropospheric NO_2 concentrations from the Copernicus Sentinel-5P satellite (2019)